IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: **Li How Chen et al.,** Art Unit No.: **1632**

Application No.: **10/082,018** Examiner: **Peter Paras Jr.**

Filed: **February 20, 2002**

For: **NOVEL MODIFIED NUCLEIC ACID SEQUENCES AND METHODS FOR INCREASING mRNA LEVELS & PROTEIN EXPRESSION IN CELL SYSTEMS**

Attorney Docket Number: **GTC-39C**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR §1.132

I, Harry Meade hereby declare and say as follows:

BACKGROUND OF DECLARANT

1. I received my Doctor of Philosophy in Biology from the Massachusetts Institute of Technology in 1977. A partial list of my scientific publications and other professional accomplishments are attached hereto as Appendix A.

2. I have been employed by GTC Biotherapeutics Inc. of Framingham, Massachusetts, since 1993. From 1994 to the present I have directed and been actively engaged in the research and development of transgenic and cloning technology.

3. Currently, I am Executive Vice President of Research at GTC-Biotherapeutics ("GTC"), formerly Genzyme Transgenics Corporation, which was until recently a subsidiary of Genzyme Corporation. One of my professional responsibilities is the development and optimization of the development of transgenic animals across a broad range of mammalian

species. As part of this responsibility I am frequently involved in efforts to improve the efficiency of nuclear transfer procedures such as those described in the above referenced patent application and have done so in more than one animal species.

4. I am one of the inventors of the above referenced patent application and have signed this declaration on my own behalf.

5. During our research, and prior to the filing of the above referenced patent application, I found that under the practices of the invention and the contemporaneous prior art that exemplification of cloning techniques in one mammalian species indicates that the same or very similar techniques are useful for the production of transgenic animals of other mammalian species. That is, techniques useful for the production of mice are also useful in the production of goats or cattle. No undue experimentation is necessary to move cloning techniques from success in one non-human mammal to another.

6. Relative to the instant application, the heart of the invention is modifying a protozoan protein so that the transgenic mammals could produce it in volume to enable the production of a vaccine. Prior to this, numerous recombinant expression systems had be tried but had been found inadequate, they simply could not express the protozoan surface protein in adequate volume. Given the degeneracy of the genetic code I and the other inventors developed a method to remove the difficulties inherent with the mammalian expression of a protozoan protein. We modified the sequence to lower the A-T content of the nucleic acid sequence, while also removing the AUUUUA mRNA instability motifs. This innovation preserved a amino acid sequence identical to the protozoan protein, but one that could be constructed by mammalian tRNA's. This technology, as described in the above referenced patent application, is and has been used in mice as a working model of transgenic non-human mammal production generally. As of this date we are preparing to go into production of the protein for a vaccine sourced from transgenic goats using the identical construct present in the mice used as examples in the above referenced application and as recited in the pending claims.

Declarant further states that the information presented above, and in the patent application referenced above, clearly demonstrates that the techniques presented and claimed within the patent application provide an answer to the problem of malaria vaccine development and do so in a way enabled across the range of non-human mammals. This is borne out by current experience, contemporaneous citations and data generated using the technology of the invention

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 9/10/04 By: Harry Meade

Harry Meade, PhD.

APPENDIX A

HARRY MEADE

PARTIAL *CURRICULUM VITAE*

EDUCATION

Received Ph.D. from MIT in 1977

Post doctoral studies at Harvard until 1979

WORK EXPERIENCE

Merck & Co. Inc. until 1981

Biogen, Inc. 1981 to 1990 focused on expression systems, first in Streptomyces, and then in the mammary gland.

Joined Genzyme in 1990 as a molecular biologist in the Transgenics Group.

Became Research Director in 1993 when GTC became an independent company.

Appointed V.P. Transgenic Research in 1994 after the merger of TSI and Genzyme Transgenics,

Appointed Executive Vice President, Research; GTC-Biotherapeutics 2002 - (formerly Genzyme Transgenics).

PARTIAL LIST OF PUBLICATIONS

Echelard Y, Meade H., Toward a new cash cow, Nat Biotechnol. 2002 Sep;20(9):881-2.

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Young MW, Meade H, Curling JM, Ziomek CA, Harvey M. Production of recombinant antibodies in the milk of transgenic animals. Res Immunol. 1998 Jul-Aug;149(6):609-10.

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Gutierrez A, Meade HM, Ditullio P, Pollock D, Harvey M, Jimenez-Flores R, Anderson GB, Murray JD, Medrano JF. Expression of a bovine kappa-CN cDNA in the mammary gland of transgenic mice utilizing a genomic milk protein gene as an expression cassette. Transgenic Res. 1996 Jul;5(4):271-9.

Gutierrez-Adan A, Maga EA, Meade H, Shoemaker CF, Medrano JF, Anderson GB, Murray JD. Alterations of the physical characteristics of milk from transgenic mice producing bovine kappa-casein. J Dairy Sci. 1996 May;79(5):791-9.

W.G. Gavin[1], D. Pollock[1], P. Fell[2], D. Yelton[2], C. Cammuso[1], M. Harrington[1], J. Lewis-Williams[1], P. Midura[1], A. Oliver[1], T.E. Smith[1], B. Wilburn[1], Y. Echelard[1] and H. Meade[1], Expression of the Antibody hBR96-2 in the Milk of Transgenic Mice and Production of hBR96-2 Transgenic Goats, THERIOGENOLOGY Vol 47, Number 1 214-219 (1997).

Paul DiTullio, Seng H. Cheng, John Marshall, Richard J. Gregory, Karl M. Ebert[1], Harry M. Meade and Alan E. Smith. Production of Cystic Fibrosis Transmembrane Conductance Regulator in the Milk of Transgenic Mice. BIO/TECHNOLOGY Vol. 10, 74-77 (January 1992).

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